

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-744

CORRESPONDENCE

I N T E R

O F F I C E

MEMO

To: NDA 20-744
From: Martin H Himmel, MD
Subject: Secondary Medical Review NDA Memo
Date: May 21, 1997
CC: HFD-570/Himmel, Pina, Wilson, Aras, Kuzmick

NDA 20-744 was submitted by Dey Laboratories on July 3, 1996 for Curosurf, a porcine derived surfactant. The proposed indication of Curosurf is "for treatment (rescue) of Respiratory Distress Syndrome (RDS) in premature infants". The package insert states that the proposed dosage is an initial dose of 1.25 or 2.5ml/kg of Curosurf, with the 2.5ml/kg dose recommended for very low birth weight infants. Up to two subsequent doses of 1.25ml/kg can be administered at 12 hour intervals if the infant remains intubated with mechanical ventilation and requires supplemental oxygen.

In support of the safety and efficacy of Curosurf, the sponsor submitted 6 phase III clinical trials (4 evaluated the drug when administered to infants already diagnosed with RDS and 2 evaluated it . Of these studies, Euro VI, which evaluated a high dose of Curosurf (initial dose of 200mg/kg followed by up to 4 additional doses of 100 mg/kg) v.s. a low dose (initial dose of 100 mg/kg followed by up to 2 additional doses of 100 mg/kg) did not show a statistically significant difference between treatment arms on any endpoints. The incidence of mortality in this trial in both treated groups was similar to that seen in treated subjects in other trials, however, because of the lack of a difference between treatment arms this trial does not support the efficacy of Curosurf. Of note, it appears that this was the only trial in the NDA in which case report forms specifically had a place for recording adverse events (as part of the action letter the sponsor should be asked if adverse events, either dosing related or non-dosing related, were collected in any of the other controlled trials in this NDA). As discussed in the medical officer review, dosing related adverse events were not prospectively defined, nor was the time frame for what would be considered dosing related stated. In addition, as the comparison is between two groups treated with the same drug, determination of the rates of dosing related adverse events is difficult, unlike for other surfactants for which placebo controlled trials have been conducted. This issue could be addressed in the future without need for conducting additional studies by stating in the package insert common dosing related adverse events seen with surfactant administration.

A second study that does not support the safety or efficacy of Curosurf is study _____ This was a trial which evaluated _____ No statistically significant differences were seen between the two treatment arms using the post audited database and, the sponsor's auditors concluded that "Due to lack of control of randomization

NDA 20-744

Page 3

May 21, 1997

The final rescue study that is of adequate size and design to support the safety and efficacy of Curosurf is Euro IV. This was a controlled, randomized, open label trial of single v.s. multiple doses of Curosurf in infants weighing 700-2000gm with RDS. Infants in the single dose group received an initial dose of 2.5ml/kg (200mg/kg) while those randomized to the multiple dose group received an initial dose of 2.5ml/kg followed by subsequent doses of 1.25ml/kg at 12 and 24 hours if their FIO₂ was greater than 21%. Regarding the endpoint of mortality at 28 days, the group receiving multiple doses of Curosurf experienced statistically significantly less mortality, both analyzed excluding patients with missing data ($P=.0528$) and including them as deaths ($P=.049$). Of note, based on the review of the case report forms by the medical officer, it appears that the subjects listed as missing data in fact died by day 28, thus, the latter analysis is the more appropriate one. There were no significant differences between treatment arms on the combined endpoint of mortality and BPD. Pneumothorax was seen significantly less often in the multiple dose group compared to the single dose group.

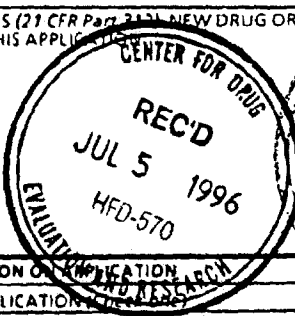
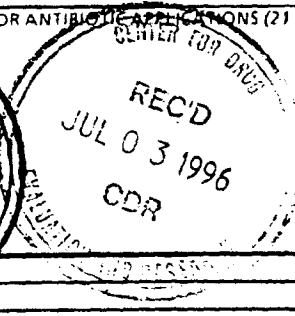
NDA 20-744

Page 5

May 21, 1997

4. The sponsor should be asked to clarify whether adverse events, either dosing related or not dosing related, were collected in any of the controlled clinical trials other than Euro VI.

APPEARS THIS WAY
ON ORIGINAL

| | | | |
|---|---|--|----------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, 314)</i> | | Form Approved: OMB No. 0910-0001 Expiration Date: December 31, 1992 See OMB Statement on Page 3. | |
| | | FOR FDA USE ONLY | |
| | | DATE RECEIVED <i>3 Jul 96</i> | DATE FILED |
| | | DIVISION ASSIGNED <i>570</i> | NDA/ANDA NO. ASS <i>20744</i> |
| NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314). | | | |
| NAME OF APPLICANT Dey Laboratories | | DATE OF SUBMISSION July 3, 1996 | |
| ADDRESS (Number, Street, City, State and Zip Code) 2751 Napa Valley Corporate Drive Napa, California 94558 | | TELEPHONE NO. (Include Area Code) 707-224-3200 | |
| | | NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (if previously issued) 20-744 | |
| DRUG PRODUCT | | | |
| ESTABLISHED NAME (e.g., USPI/USAN) poractant | | PROPRIETARY NAME (if any) Curosurf ^R | |
| CODE NAME (if any) BAN: Poractant alpha | CHEMICAL NAME (major components) 1,2 diacyl-sn-glycero-3-phosphorylcholine Refer to NDA Vol. 1.2 pages 3-7 for all chemical names | | |
| DOSAGE FORM Suspension | ROUTE OF ADMINISTRATION Intra-tracheal | | STRENGTH(S) 80 mg/mL |
| PROPOSED INDICATIONS FOR USE Curosurf is indicated for _____ and treatment (rescue) of Respiratory Distress Syndrome (RDS) in premature infants. | | | |
| LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 314.10), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION: | | | |
|   | | | |
| INFORMATION ON APPLICATION | | | |
| TYPE OF APPLICATION | | | |
| <input checked="" type="checkbox"/> THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) <input type="checkbox"/> THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55) | | | |
| IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION | | | |
| NAME OF DRUG | | HOLDER OF APPROVED APPLICATION | |
| TYPE SUBMISSION (Check one) | | | |
| <input type="checkbox"/> PRESUBMISSION | | <input type="checkbox"/> AN AMENDMENT TO A PENDING APPLICATION | |
| <input checked="" type="checkbox"/> ORIGINAL APPLICATION | | <input type="checkbox"/> RESUBMISSION | |
| SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv)) _____ | | | |
| PROPOSED MARKETING STATUS (Check one) | | | |
| <input type="checkbox"/> APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) | | <input type="checkbox"/> APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC) | |

INTEROFFICE MEMO

TO: NDA 20744
FROM: C. Joseph Sun, Ph. D.
SUBJECT: Team Leader NDA Review Memo
DATE: May 29, 1997



5/29/97

See pharmacologist review for a summary of pharmacology and toxicology data in this application.

I concur with the pharmacologist's conclusion that the pharmacology and toxicology of Curosurf have been studied for the proposed indication and that the drug is approval from a preclinical standpoint.

Curosurf is a natural lung surfactant extracted from pig lungs. It has been shown to lower surface tension in in vitro tests and it improved tidal volume, lung compliance and survival of immature preterm rabbits. The administration of Curosurf with radiolabeled phospholipids into the lung of adult and new born rabbits resulted in the presence of 50 % of radioactivity in the lung alveolar lining 3 hours later. However, very little radioactivity was found in alveolar macrophages or any major organs at 48 hours.

Subchronic toxicity studies were performed in rabbits (14 days, intratracheal), dogs (14 days, intratracheal) and rats (14 days, intratracheal and 4 weeks, intraperitoneal). Lung was the target organ of effect by intratracheal route in rabbits and dogs. In rats no effects were reported following intratracheal administration whereas liver was the target organ of toxicity by intraperitoneal route.

Curosurf was negative in all 5 genotoxicity studies (Ames assay, gene mutation assay in Chinese hamster V79 cells, chromosomal aberration assays in Chinese hamster ovary cells, unscheduled DNA synthesis in human HeLa S3 cells and in vivo micronucleus test in mice).

Due to its intended population and short term usage, reproductive studies and carcinogenicity studies are not required for an NDA approval.

There is no outstanding preclinical issue.

Cc: Orig. NDA
HFD-570/Division file
HFD-570/Sun
HFD-570/Kuzmik

APPEARS THIS WAY
ON ORIGINAL

Memorandum

To: NDA 20-744

From: L. Miriam Pina, M.D.
Division of Pulmonary Drug Products, HFD-570

Through: Martin Himmel, M.D.
Deputy Director
Division of Pulmonary Drug Products, HFD-570

Date: May 16, 1997

Subject: Curosurf, method of administration.

This memo is to clarify the method employed to administer Curosurf at each clinical site for each pivotal trial submitted to the NDA. The sponsor was asked to clarify this procedure, how the surfactant was actually administered and, if both methods were used, how many patients used each method, due to the inconsistency found between the method of administration proposed in the protocols, i.e., the dose was to be given in divided bolus to each main bronchus, and the method said to have been used in the published study reports, i.e., the dose was given either as a single bolus or in divided bolus to each main bronchus.

This clarification was important for the assessment of the data that support the methods of administration recommended in the labeling.

The following table shows the distribution of the methods used to administer Curosurf for each trial.

Method of Administration of Curosurf by clinical trial.

| CLINICAL TRIAL | NUMBER OF PATIENTS | | |
|-------------------|--------------------|------------------|---------------|
| | Single Bolus | Divided Bolus | Unknown |
| EURO I (N=145) | 14 (1 center) | 125 (6 centers) | 6 (1 center) |
| EURO III (N= 195) | 160 (22 centers) | 31 (4 centers) | 4 (2 centers) |
| EURO IV (N= 357) | - | 357 (15 centers) | - |
| EURO VI (N= 2168) | - | 2110 (? centers) | 58 |
| Total | 174 | 2878 | 68 |

Discussion.

The additional information submitted to the NDA by the sponsor on May 15, 1997, shows that a total of 23 centers used the single bolus technique to administer Curosurf to 174 patients, and more than 100 centers gave Curosurf, to 2878 patients, in a divided bolus fashion.

The method used in the trials that support the efficacy claims, i.e., EURO III, EURO IV, and the , is as follows: EURO III mostly used the single bolus technique (although 4 centers used the divided bolus method); while the other two trials (EURO IV and the used the divided bolus technique only.

Even though the divided bolus technique was the method of administration most widely used among the centers, the data above show that both techniques are supported by pivotal trials that showed evidence of significant efficacy in clinically relevant parameters.

Conclusion.

Both techniques have enough support in the pivotal trials, therefore both can be recommended in the labeling if the NDA is approved.

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-744

SEP 3 1998

Dey Laboratories
271 Napa Valley Corporate Drive
Napa, California 94558

Attention: Peggy J. Berry
Regulatory Affairs Manager

Dear Ms. Berry:

Please refer to your new drug application (NDA) dated July 3, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Curosurf (poractant) Intratracheal Suspension.

We acknowledge receipt of your submissions dated March 3 and 19, April 7 and 21, May 15, and July 13 and 28, 1998. Your submission of March 3, 1998 constituted a full response to our July 3, 1997, action letter. The user fee goal date for this application is September 4, 1998.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following issues.

THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE

10 pages

The test for color is not adequate in that the specifications are too broad. In addition, the Agency was anticipating a When the original request was made in the July 3, 1997 Letter from the Agency.

Response:

DEY LP and Chiesi Farmaceutici, S.p.A., hereby make a commitment to the following actions concerning the color test for the Curosurf Drug Substance and Drug Product:

1. To further evaluate the visual color method currently in use to determine if the method can be improved through the use of additional or different color standards (to improve the ability of the method to discriminate by improving the scale).
2. To evaluate the use of an instrumental method (e.g. _____ for the determination of color and determine if such a method is superior to the current visual method or an improved visual method.
3. To submitted a summary of the evaluations together with supporting data within 6 months of approval of the Curosurf NDA 20-744. In the event that a new method or a method with improved discrimination is achieved, either visual or instrumental, a copy of the method and supporting validation will also be submitted with a request to implement the new/revised method upon approval of the FDA.

APPEARS THIS WAY
ON ORIGINAL



DUPLICATE

DEY LABORATORIES
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL (707) 224-3200 FAX (707) 224-0791

21 September 1998

John Jenkins, M.D., Director
Division of Pulmonary Drug Products (HFD-570)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 10B-03
5600 Fishers Lane
Rockville, MD 20857

VIA FEDERAL EXPRESS
(301)827-1050

RE: NDA 20-744
Curosurf[®] (poractant alfa) Intratracheal Suspension
USAN Statement of Adoption

Dear Dr. Jenkins:

Enclosed please find a copy of the USAN Council Statement of Adoption of poractant alfa as the United States Adopted Name for Curosurf[®].

If you have any questions please contact me at (707) 224-3200 ext. 475.

Sincerely,

/S/

Peggy J. Berry
Regulatory Affairs Manager

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL





UNITED STATES ADOPTED NAMES COUNCIL

RUTA FREIMANIS, Pharm.D., R.Ph., Secretary
(312) 464-4045

American Medical Association
515 North State Street
Chicago, Illinois 60610

Telefax: 312-464-4184

April 29, 1998

KK-11

Chiesi Pharmaceuticals Inc.
115 College Street
Burlington, VT 05401

Attn: Bruce Thompson
Director, Regulatory Affairs

Dear Mr. Thompson:

It is my pleasure to inform you that the USAN Council adopted **poractant alfa** as the United States Adopted Name for Chiesi Pharmaceuticals' pulmonary surfactant identified as an extract of porcine lung, trademarked Curosurf.

Enclosed is a copy of the Statement of Adoption on **poractant alfa**. Please review this information for accuracy, initial and return the statement to me within 45 days from the date listed above. The information then will be forwarded to the C.V. Mosby company for publication in the journal of *Clinical Pharmacology and Therapeutics* and to the United States Pharmacopeial Convention, Inc., for publication in the *USP Dictionary of USAN and International Nonproprietary Names*.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Ruta Freimanis, PharmD
Secretary
USAN Council

RF/drl

Enclosure: N98;33

Toyer

RECORD OF TELEPHONE CONVERSATION

NDA: 20-744 DATE: April 6, 1999
APPLICANT: Dey Laboratories
DRUG: Curosurf (poractant) Intratracheal Suspension
INITIATED BY: X APPLICANT FDA
NAMES AND TITLES OF PERSONS WITH WHOM CONVERSATION WAS HELD:
Dr. Jean Nashed, Dr. Denise Toyer, and Dr. Brenda Uratani
APPLICANT: Mr. Bruce Thompson (Chiesi for Dey)
TELEPHONE #: 802-658-8811
IMTS# 4015

BACKGROUND

During the review of this application the Division and Chiesi/Dey have had communications regarding data pertaining to the container closure system. This teleconference was requested by Chiesi/Dey to discuss Comment 5, of the September 3, 1998, approvable letter. For further background information see chemistry, manufacturing, and control reviews one and two; the July 3, 1997, not approvable letter (comment 7d); and the September 3, 1998 approvable letter (comment 5).

TELECON

In prior communications the Division requested that Chiesi provide a detailed description of the acceptance protocol for the container closure system. We note that it appears that Chiesi does not clean the stoppers once they are received from the manufacturer. The Division indicated that in order to have good control over the stoppers, Chiesi must have appropriate acceptance criteria and adequate sample testing.

Chiesi indicated that they conduct several tests on the incoming stoppers and that the full protocol will be submitted. The following tests were given as an example.

1. Particulate Matter USP test that is capable of detecting the presence of silicon particles;
2. USP Heavy Metals
3. Extractable's testing; and
4. Sterility

The Division noted that pyrogens from the stoppers could be removed by _____

. The Division also noted that the acceptance protocols for the vials and the stoppers must be different if Chiesi conducts different post-acceptance processing on each. For example, since Chiesi _____ vials limited acceptance testing is required for the vials. However, if Chiesi does not _____ the stoppers then appropriate acceptance testing must be conducted. The Division reminded Chiesi that testing for silicon particles, pyrogens, and dimensional testing must be a part of the acceptance protocol.

Chiesi noted that they would have to clarify whether the supplier of the stopper is conducting pyrogen testing and ensure that the supplier is providing an adequate certificate of analysis

(COA). Chiesi will provide a short summary of cleaning and testing responsibilities for the container/closure system indicating who (Chiesi or supplier) is responsible for each stage of the purification and testing process. This will include a detailed description of the acceptance testing protocol with a sampling plan for stoppers and a copy of the appropriate COAs for stoppers and vials. The above information will be included in Dey's response to the September 3, 1998, approvable letter. Chiesi expects to forward their responses to the approvable letter, to Dey, within the next 30 days. Dey will then compile the complete response and forward to the Division.

/S/

Denise Toyer, R.Ph., Pharm.D.
Project Manager

cc:

Orig. NDA

HFD-570/Division File

HFD-570/Urutani/4-12-99

HFD-570/Nashed/4-12-99

HFD-570/Toyer

Initialed by: Schumaker/4-9-99

APPEARS THIS WAY
ON ORIGINAL

120200K

MAR 27 1998

NDA 20-744

Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, California 94558

Attention: Peggy Berry
Regulatory Affairs Project Manager

Dear Ms. Berry:

We acknowledge receipt on March 4, 1998, of your March 3, 1998, resubmission to your new drug application (NDA) for Curosurf Intratracheal Suspension.

This resubmission contains responses to each item from our July 3, 1997, action letter.

We consider this a complete, class 2 response to our July 3, 1997, action letter. Therefore, the user fee goal date is September 4, 1998.

If you have any questions, contact Ms. Betty Kuzmik, Project Manager, at 301-827-1051.

Sincerely yours,

Betty Kuzmik
Project Manager
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION

NDA: 20-744

DATE: February 10, 1998

SPONSOR: Dey labs

DRUG: Curosurf

INITIATED BY: X APPLICANT

 FDA

NAMES OF PERSONS WITH WHOM CONVERSATION WAS HELD:

Chiesi: Bruce Thompson

FDA: Betty Kuzmik, Jean Nashed

Background


Reference is made to the sponsor's January 16, 1998, telephone facsimile (fax) in which a conference call is requested to discuss the CMC portions (#6-9) of the Agency's NA letter dated July 3, 1997, as well as the extent and format of the required safety update. Reference is also made to the January 19, 1998, fax which includes a list of the questions and issues for discussion; the January 22, 1998, telecon with members from Dey Labs, Chiesi, and this Division; the minutes of that telecon; and the February 9, 1998 fax (attached) in which clarification of the minutes is requested.

Telecon

1. As stated in the February 9, 1998, fax and as conveyed by Dr. Thompson, point 4 of the meeting minutes deals with expression of test results as "mg/mL." Dr. Nashed clarified that it is acceptable for the sponsor to use the average Mol. Wt. of each phospholipid to express the result as **mg phospholipid "x"/mL** (the second option).

The following other conclusions were reached after discussion.

2. The specifications for each phospholipid should be based on actual data for corresponding individual phosphorus levels in the batch, not a recalculation from the specification range of total phosphorus level.
3. The references for methods on the specification sheet should be updated to the last submission.
4. The sponsor will include data on the methods at the newly finished manufacturing site for the bulk substance as well as data on media fill and batch results.


Betty Kuzmik
Project Manager

L. 1000

RECORD OF TELEPHONE CONVERSATION

NDA: 20-744

DATE: January 22, 1998

SPONSOR: Dey labs

DRUG: Curosurf

INITIATED BY: X APPLICANT FDA

NAMES OF PERSONS WITH WHOM CONVERSATION WAS HELD:

Dey Labs: Allan Kaplan, Randy Miller, Peggy Berry

Chiesi: Bruce Thompson

FDA: Betty Kuzmik, Jean Nashed, Miriam Pina, Guirag Poochikian

Background

Reference is made to the sponsor's January 16, 1998, telephone facsimile (fax) in which a conference call is requested to discuss the CMC portions (#6-9) of the Agency's NA letter dated July 3, 1997, as well as the extent and format of the required safety update. Reference is also made to the January 19, 1998, fax (attached) which includes a list of the questions and issues for discussion.

Telecon

Clinical issues

Dr. Pina stated that the safety update should contain any information available from Europe on safety (adverse events reported by consumers, complications of treatment from ongoing trials, etc.) that could affect product labeling. She requested that this information be submitted in tabular format. It may be submitted as soon as the information is available and should cover the period from the last safety update to the time of submission.

Dey Labs stated that the clinical audits are nearly complete. Source data have been confirmed on almost all of the patients. The revised Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) are scheduled for submission at the end of February 1998.

CMC issues

Dey Labs stated that Chiesi (the manufacturer) is now ready for GMP inspection. Dr. Nashed replied that the FDA inspection will be requested once the full response from Dey Labs is received.

With regard to the sponsor's proposals in the January 19, 1998, fax, Dr. Nashed responded that the FDA's position remains as stated in the July 3, 1997, letter. Any modifications or other proposals that the sponsor wishes to make must have data to support them as well as the rationale for the proposals. This

should be submitted with the full response. The proposals will be reviewed in detail at that time.

Specific issues discussed were as follows:

1. Testing performed on bulk suspension vs filled vials

Dr. Nashed indicated that it is preferable to have testing performed on the filled vials. If testing were performed on the bulk suspension, there would have to be a clear and reliable "link" to some testing that is performed on the filled vials. Also, the manufacturing time frame from the bulk suspension to the final filled vials has to be restricted and clearly specified. Alternatively, FDA will accept all testing performed on the filled vials and testing on the bulk suspension can be treated as in-process tests.

2. Tightening of specifications

FDA stated that they consider _____ to be an important issue. They believe that the specification for it should be tightened. They indicated that in the data available for review, only one batch fell within the upper range of the specification so tightening the specification should not present an issue. They stated that if additional data are available that suggest otherwise, that data should be provided along with the response submission.

Regarding other specifications that were proposed by Dey Labs to remain unchanged from the original submission, FDA stated that complete analytical results on the NDA and subsequent batches should be submitted with a rationale for either changing or retaining the specification as presented in the original submission. These will be review issues.

3. Extractable volume

FDA indicated that unnecessary overfills cannot be permitted and that the amount of overfill necessary to meet the label claim extraction should be revisited. If data are available which suggest a different approach, they should be submitted with the full response. FDA suggested using USP chapter <1> on Injections as a reference. It would be helpful to look and provide for data on the viscosity of the drug.

4. Expression of test results as mg/mL

FDA commented that for dry drug substance, expression as a % of _____ is acceptable. However, for drug product, an expression of mg/mL should be provided. FDA agreed that some

natural variability of the molecular weight (MW) may occur but there must be greater control of batch-to-batch reproducibility than specifications expressed as a range-of-a-range value. It was recommended that specifications be expressed in mg/mL and have additional percentage restriction in relation to the

e.g., 1.8-2.2 mg/mL and 65-75% of total

Dey Labs should also provide a properly validated method to ensure that the calculation is consistently performed.

/S/

Betty Kuzmik
Project Manager

cc:

NDA 20-744

HFD-570/Division File

HFD-570/Kuzmik/2-2-98

HFD-570/Pina/2-4-98

HFD-570/Nashed/2-3-98

HFD-570/Poochikian/2-3-98

APPEARS THIS WAY
ON ORIGINAL

Kuzmik

RECORD OF TELEPHONE CONVERSATION

NDA: 20-744

DATE: Sept 18, 1997

SPONSOR: Dey labs

DRUG: Curosurf

INITIATED BY: X APPLICANT

 FDA

NAMES AND TITLES OF PERSONS WITH WHOM CONVERSATION WAS HELD:

Dey Labs: Allan Kaplan, Randy Miller, Debbie Perez, Peggy Berry

Chiesi: Hubert Loncin, Bruce Thompson

FDA: Betty Kuzmik, Miriam Pina

TELEPHONE #:

INTS #: 1735

Background

Reference is made to the sponsor's September 8, 1997 submission (attached) in which clarification is requested on comments #1, #3, and #4 of the Agency's NA letter dated July 3, 1997.

Telecon

The following were discussed and clarified.

1. **100% audits of Euro I, III, IV, and studies**

Dr. Pina explained that the purpose of the request to audit the patients in Euro I who were not fully audited by the contractors is to allow Dey Labs to acquire more data that could improve the results obtained on the mortality endpoint. The sponsor stated that they are not optimistic that a second search will provide any new information but they plan to give it their best effort. Dey Labs will try to locate source documents for their audits of all the trials.

Dr. Pina also stated that FDA requires source data to correlate with the data base submitted to FDA.

3.. **Review of hospital records for all patients with missing mortality data**

Dr. Pina pointed out that the determination as to whether all patients with missing mortality data were alive or dead at day 28 may be accomplished with source documentation. Even if there are no hospital records, she suggested searching for death certificates, autopsy reports, nursing notes, laboratory records, records of clinic visits after discharge from the hospital, etc.

4. **Updated study reports and updated integrated summaries**

Dr. Pina stated that the results of each individual trial

should be updated as well as the integrated summaries of safety and efficacy. Regardless of whether Dey Labs submits an addendum to the current summaries or revised summaries, a full report with full data supporting their conclusions is required. She also requested that documentation of each one of their determinations be submitted.

Dey Labs voiced their appreciation to Dr. Pina for her clarification as they are now in the midst of initiating the audits.

NOTE: I called Ms. Perez after this telephone conference to request that Dey Labs call the Agency before submitting any data. She agreed.

/S/

Betty Kuzmik
Project Manager

cc:

NDA 20-744

HFD-570/Division File

HFD-570/Kuzmik/9-19-97

HFD-570/Pina/9-20-97

APPEARS THIS WAY
ON ORIGINAL



DEY LABORATORIES
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL (707) 224-3200 FAX (707) 224-0791

September 8, 1997

Dr. E. Nashed
Division of Pulmonary Drugs
HFD-570
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-744
Curosurf Intratracheal Suspension
Action Letter (July 3, 1997)

Dear Mr. Nashed:

The comments of the Curosurf NDA Action Letter (3 July, 1997) concerning the clinical studies have been reviewed. Preparations are being made to perform clinical site audits, however, there are a few items, listed below, which will need clarification and confirmation of prior to initiation of these audits.

Point 1: 100% audits of Euro I, III, IV.

-The comment makes reference to "10 patients in the Euro I study who were not fully audited by your contractors".

The original audit plan for Euro I included a 100% audit of the patients. The only Euro I patients who did not have audited source documentation were those patients for whom original source documentation (i.e. hospital records) could not be located at the clinical sites.

We are evaluating other means of verifying information for these patients (e.g. death certificates), however, we do not anticipate finding additional data at the sites for these patients. Therefore, it is our intention that the CRFs for these patients will be considered the available source documents and the data from these CRFs will be used in the analysis.

-The comment makes reference to "All discrepancies between the data submitted in the original NDA and the data derived from the full audit of these four studies..."

In the additional auditing that will be performed for these studies, we are considering comparing the source data directly to the database which was originally submitted. In instances where there is conflict between the source data and the database, we will also review the corresponding CRF (i.e. CRFs will only be reviewed against source data if there is a discrepancy between source data and the database.). Do you consider this strategy valid in addressing the Agency request?

Point 2: No clarification needed.

Point 3: Review of Hospital Records for all patients with missing mortality data

-The comment makes reference to "patients.... with missing mortality data".

Dr. Nashed
Curosurf
Page 2
August 27, 1997

Are you referring to CRFs or source documentation reviewed in the clinical site audits?

-The comment makes reference to inclusion of "appropriate supporting documentation".

We interpret this to mean copies of any available source documents which could substantiate that the patient was alive or dead before or after day 28. Do you anticipate any specific documentation to support this determination?

Point 4: Updated Study Reports and Updated Integrated Summaries

-The comment requests the generation and inclusion of updated study reports based on the fully audited database.

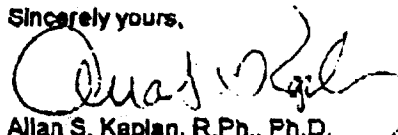
We have reviewed this request in the context of when the studies were conducted, and the use of post-hoc auditing for interpretation of data. The reports submitted in the original NDA were either reports prepared by the Investigators or reprints. No study reports were generated specifically for this NDA.

We would like clarification on the Agency's request for updated study reports to be prepared for this NDA, given the fact that we will be providing updated integrated summaries of efficacy and safety.

We are in agreement that the Integrated Summaries of Safety and Efficacy will need to be updated if data discrepancies are found during the full audit of the sites. This updating will be in the form of an addendum to the current summaries, if there is little impact from the full audits. If the full audits uncover discrepancies which impact the majority of the summary information or impact study conclusions, revised summaries will be provided.

If you require clarification, or additional information, please contact me at (707) 224-3200, ext. 229.

Sincerely yours,



Allan S. Kaplan, R.Ph., Ph.D.
Vice President of Technical Affairs

dp
cc: Betty Kuzmik, Food and Drug Administration

RECORD OF TELEPHONE CONVERSATION

NDA: 20-744

DATE: August 1, 1997

SPONSOR: Dey labs

DRUG: Curosurf

INITIATED BY: X APPLICANT

FDA

NAMES AND TITLES OF PERSONS WITH WHOM CONVERSATION WAS HELD:

Dey Labs: Allan Kaplan, Clara Dickinson

FDA: Betty Kuzmik, Jean Nashed

TELEPHONE #:

Background

Reference is made to the sponsor's July 31, 1997 submission (attached) in which clarification is requested on point 6.b. of the Agency's NA letter dated July 3, 1997.

Telecon

Dr. Nashed stated that the proposed method which involves

on the surface as a means of quantitative determination of color. She emphasized that they need to validate the methodology they choose and include it in their full response.

Betty Kuzmik
Project Manager

CC:

Orig. NDA

HFD-570/Division File

HFD-570/Kuzmik/8-25-97

HFD-570/Nashed/8-26-97

APPEARS THIS WAY
ON ORIGINAL



DEY LABORATORIES
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL (707) 224-3200 FAX (707) 224-0791

July 31, 1997

Dr. E. Nashed
Division of Pulmonary Drugs
HFD-570
Office of Drug Evaluation/II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

RE: New Drug Application 20-744
Curosurf Intrathecal Suspension

Dear Dr. Nashed:

Reference is hereby made to NDA 20-744 for Curosurf Intrathecal Suspension submitted on July 3, 1996 and the FDA letter of July 3, 1997 issued on this NDA.

Specifically, we would like to request clarification on point 6.b of the aforementioned letter.

We have been evaluating the use of a _____ in determining color on a quantitative basis. The lipophilic nature of the drug substance and drug product prevent us from preparing aqueous solutions (only suspensions are possible in water). Therefore, we have been working with _____ solutions, similar to the steps for preparation of the product. The drawback has been the unavailability of color standards which can be prepared as _____ solutions (important for _____ using the _____). The color standards in the USP are aqueous solutions.

We have also evaluated the use of _____ against color standards. This involved the comparison of the samples (_____ solutions) to standard color solutions (aqueous solutions). We believe we will be able to set-up a specification such that the color of the sample will be between two color standards. The stability specification may involve different color standards; but we will need to evaluate this further.

We would like to inquire if this _____ to color standards is an acceptable means of quantitative determination of color in accordance with the FDA's request.

If you require clarification or additional information, please do not hesitate to contact me directly at 707-224-3200, extension 229.

Sincerely yours,

Allan S. Kaplan, R.P., Ph.D.
Vice President of Technical Affairs

cl
cc: Betty Kuzmik, Food and Drug Administration



DEY LABORATORIES
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL (707) 224-3200 FAX (707) 224-0701

July 31, 1997

John Jenkins, M.D.
Director
Division of Pulmonary Drugs
HFD-570
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

RE: New Drug Application 20-744
Curosurf Intrathecal Suspension
Change of Signatory Authority

Dear Dr. Jenkins:

Reference is hereby made to NDA 20-744 for Curosurf Intrathecal Suspension submitted on July 3, 1996.

It should be noted that all post-NDA filing submissions have been signed (cover letter and FDA Form 356h) by our Contract Research Organization,

By way of this correspondence, we are advising the Food and Drug Administration that all future submissions for NDA 20-744 will be submitted under the signature of Dr. Allan S. Kaplan, Vice President of Technical Affairs.

If you require clarification or additional information, please do not hesitate to contact me directly at 707-224-3200 extension 229.

Sincerely,

Allan S. Kaplan, R.P., Ph.D.
Vice President of Technical Affairs

cl



Lipha Americas Company

None

FDA

12-5# 1484

APPEARS THIS WAY
ON ORIGINAL

Post-Telecon Comment:

One set of specifications can be used with appropriate indications when different release specifications are used, e.g.,

| Parameter | Specification (Specification at release) | Method | Method Description Vol/Page (Date of submission) | Method Validation Vol/Page (Date of submission) |
|-----------|--|--------|---|---|
| | | | | |
| | | | | |

cc:

Orig NDA 20-744

HFD-570/Div

HFD-570/Kuzmik/7-15-97

HFD-570/Nashed/7-15-97

n:\nda\20744\pm\97-07-11.tel

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT

C O V E R
S H E E T

FAX

To: Betty Kuzmik
Fax #: 301-827-1271
Subject: Curosurf NDA 20-744: Action letter of July 3, 1997
Date: July 10, 1997
Pages: 1, including this cover sheet.

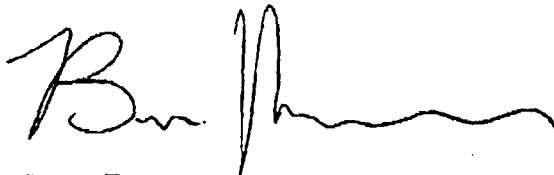
COMMENTS:

Further to your discussion with I would like to get clarification on the reference to "release specifications" in the action letter (e.g. page 7, point #8). The NDA contains "Regulatory Specifications" which pertain to the shelf-life of the marketed product (NDA vol. 1.4, pg 3). By definition, the Regulatory Specifications are those which the product must meet during its shelf-life at the labeled storage conditions. Release Specifications, as we define them, are the specifications which are used to release the product to market and are not necessarily the same as Regulatory Specifications, because of inherent changes during shelf-life of the product.

The Guideline for the Format and Content of the Chemistry, Manufacturing and Controls section of an Application, Pg. 8, Item F: Specifications and Analytical Methods for the Drug Product requires the submission of Regulatory Specifications.

I would appreciate your help in addressing this issue.

Regards,


Bruce Thompson

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION

NDA NUMBER: 20-744

DATE: March 5, 1997

INITIATED BY: APPLICANT

 x FDA

FIRM NAME: Dey Laboratories

DRUG NAME: Curosurf

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:

Randall Miller, Dey Laboratories; Diane Mitrione, BioPharm;

Jean Nashed, FDA chemist, and Betty Kuzmik, Project Manager, FDA

This telecon was convened to discuss preliminary chemistry and microbiology review comments from the Curosurf NDA.

Dr. Nashed stated that the CMC portion of the NDA is still under review. Written comments will be sent to the sponsor by the end of March in the form of a letter but to expedite the sponsor's ability to respond before an action letter is issued, the following preliminary comments and requests for information were conveyed with this telecon.

The most crucial concerns are as follows:

Additional chemistry and microbiology comments will be provided in a letter. After addressing all issues, the application should be amended with updated information and tables, including page/volume reference to methods and methods validations.

The sponsor agreed to discuss these requests with Chiesi next week and provide the most crucial information as soon as possible.

/S/

Betty Kuzmik

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 03-Oct-1996 09:43am EST
From: Denise Toyer
TOYERD
Dept: HFD-570 PKLN 10B45
Tel No: 301-827-1091 FAX 301-827-1271

TO: Betty Kuzmik

(KUZMIKB)

Subject: CUROSURF

Dr. Randall Miller from Dey called on 10/3/96 with the following information:

is no longer with the company. All correspondence concerning the NDA should be directed to:
Dr. Randall Miller at 707-224-3200-ext.423. 296

He has talked with you and Dr. Pina regarding the clinical issues but has not talked to Dr. Nashed regarding any chemistry issues. He wanted to know if there were any pending chemistry issues that needed to be discussed. I spoke with Dr. Nashed and she wanted me to inform Dr. Miller that the review is ongoing at the present time and she does not need any information from him. She will contact him if this changes. I gave this message to Dr. Miller's secretary on 10/7/96.

Thanks.

De 'se.

APPEARS THIS WAY
ON ORIGINAL

OCT 18 1996

RECORD OF TELEPHONE CONVERSATION

NDA NUMBER: 20-744

DATE: October 18, 1996

INITIATED BY: _____ APPLICANT

____x____ FDA

FIRM NAME: Dey Laboratories

DRUG NAME: Curosurf

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
of Dr. Miller's office

TELEPHONE NUMBER: 707-224-3200 ext 423

I asked _____ to have Dr. Miller send a comprehensive list of all manufacturing facilities for the drug substance, bulk drug substance, and drug product. The list should include the detailed address, person to contact, telephone and fax number as well as the responsibility at each facility. All processes up to the final drug product packaged in the carton should be included. If the drug product is packaged in different facilities, each facility will have to be inspected. The information should be included for batches manufactured for both the to-be-marketed drug product and drug product used in the pivotal clinical trials. If possible the Central File Number (CFN) for each site should be included.

JS/

Cathie Schumaker

cc:

Orig NDA 20-744

HFD-570/Div

HFD-570/Kuzmnik

HFD-570/Nashed

APPEARS THIS WAY
ON ORIGINAL

Kuzmik

NDA 20-744

JUL 11 1996

Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

Attention: Katherine A. Gold
Director, Regulatory Affairs

Dear Ms. Gold:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Curosurf (poractant)

Therapeutic Classification: Standard

Date of Application: July 3, 1996

Date of Receipt: July 3, 1996

Our Reference Number: NDA 20-744

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 1, 1996 in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact:

Betty Kuzmik
Project Manager
Telephone: (301) 827-1051

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

 7/11/96

Cathie Schumaker
Chief, Project Management Staff
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

MAY 28 1996

IND

Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, California 94558

Attention: Katherine A. Gold
Manager, Regulatory Affairs

Dear Ms. Gold:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Curosurf.

Reference is also made to the April 26, 1996 telephone conference between Mr. Bruce Thompson from Chiesi Pharmaceuticals Inc, Dr. Randall Miller, Dr. Allan Kaplan, and yourself from Dey Labs, and Dr. James Bilstad from the Office of Drug Evaluation II, Dr. John Jenkins, Dr. Jean Nashed, and Ms. Betty Kuzmik from this Division.

At that telephone conference, we informed you that the Agency has determined, based on the information currently available, that Curosurf and Survanta are considered the same drug from the standpoint of the Orphan Drug Regulations. The rationale supporting this decision is that, in contrast to drugs composed of small molecules to which the concept of an active moiety (21 CFR 316.3(b)(2)) applies, surfactants are a complex mixture of both large and small molecules, many of which have poorly defined specific or unique physiologic functions. As such, surfactants are most like the macromolecules in that it would be trivially easy to make minor changes in a surfactant that would leave the activity of the drug unaltered, but would create a "new drug" if the micromolecular definition of active moiety were applied. The Agency believes that the paradigm of macromolecules should be applied to surfactant drugs. 21 CFR 316.3(b)(13)(ii)(D), states that "Closely related, complex partly definable drugs with similar therapeutic intent,.... would be considered the same unless the subsequent drug was shown to be clinically superior." Therefore, based on currently available data, we conclude that Curosurf and Survanta should be considered the "same drug."

BEST POSSIBLE COPY

IND
Page 2

As we discussed, should you wish to apply the "active moiety" concept to a particular component of surfactants, you would need to demonstrate both that the particular component is present and active in one surfactant and that it is either not present or present at levels that are inactive in the other surfactant. As discussed in the Federal Register of December 29, 1992 (57 FR 62077), different in vitro biologic activity will not normally suffice to support a claim of clinical superiority because of concern that in vitro activity may not correlate with clinical effects. As such, any in vitro or pre-clinical models used to support the activity of individual components of surfactants should be well correlated with clinical effects.

Sincerely,

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug evaluation II
Center for Drug Evaluation and Research

CC:
IND
HFD-570/Div File
HFD-570/Pina
HFD-570/Himmel
HFD-570/Nashed
HFD-570/Poochikian
HFD-570/Gebert
HFD-570/Wilson
HFD-570/Choi
HFD-570/Sun
HFD-570/Schumaker/5-21-96
HF-35/Mccormick
GCF-1/Dickinson
R/D by MHimmel
Draft letter typed by Bkuzmiki/5-14-96 and 5-21-96
Reviewed by Drs. McCormick, Jenkins, Bilstad, and
Ms. Dickinson/5-21-96
f/t by: VSmith 5-23-96

APPEARS THIS WAY
ON ORIGINAL

ISI

5/23/96

Kuzmik

RECORD OF TELEPHONE CONVERSATION

NDA: #

DATE: April 26, 1996

DRUG: Curosurf

INITIATED BY: APPLICANT

 FDA

DEY LABS: Katherine Gold, Randy Miller, Allan Kaplan

FDA: Jim Bilstad, John Jenkins, Marty Himmel, Jean Nashed, and Betty Kuzmik

TELEPHONE #: 707-224-3200, ext 217

Background

Refer to minutes of the March 15, 1996 internal Division meeting and minutes of the March 19, 1996 telephone conversation with the sponsor.

Telecon

Dr. Jenkins communicated to the sponsor that the Agency has decided, in a meeting two days ago involving the center director, that Survanta and Curosurf are the same drug according to the Orphan Drug Regulations. In order to prove that they are different, the sponsor must demonstrate that the different amounts of ingredients in Survanta and Curosurf make a difference in the activity of the drug, i.e., if Survanta has less of one ingredient than Curosurf, Dey Labs must show that the ingredient is not necessary for the activity of Survanta. They must also show that levels of that same ingredient in Curosurf contribute to Curosurf's activity. The sponsor must provide well validated tests and methods to demonstrate this as well as data to demonstrate its relevance to clinical effects of the drug. It is not enough to show that they are different based on the quantity of their ingredients.

Curosurf will be blocked from approval until the expiration date of Survanta's exclusivity (July 1998). This is not a basis for refusing to file the Curosurf application, however, when it is submitted. The Division will review it as it would any other NDA with a user fee cycle. If the application reaches the approvable stage, the Division may be able to approve it pending the expiration of Survanta's exclusivity. This is currently being explored.

Dr. Jenkins further stated that all naturally derived surfactants have been deemed the same, including Infasurf. This means that, unless the above requirements are met for demonstrating difference, neither Infasurf nor Curosurf will be granted orphan drug exclusivity when Survanta's expires.

As requested by Dey Labs, an Agency letter will be issued that provides an explanation for how this decision was reached.

/S/

Project Manager

cc: IND #
HFD-570/Division File
HFD-570/Kuzmik
HFD-570/Himmel/5-3-96
HFD-570/Pina
HFD-570/Nashed
HFD-570/Poochikian
HFD-570/Choiy
HFD-570/Sun
HFD-570/Jenkins/5-6-96

APPEARS THIS WAY
ON ORIGINAL